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| EXAMINER | |
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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Application Number: 10/573,606
Filing Date: March 28, 2006
Appellant(s): KLAVENESS ET AL.

Craig M. Bohlken
Reg. No. 52,628
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 6/7/10 appealing from the Office action mailed 1/5/10.

**(1) Real Party in Interest**

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

The following is a list of claims that are rejected and pending in the application:

Claims 15-18,20,21 and 23-25 are pending in the application. Claims 15-18,20,21 and 23-25 are rejected.

**(4) Status of Amendments After Final**

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

**(5) Summary of Claimed Subject Matter**

The examiner has no comment on the summary of claimed subject matter contained in the brief.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the

subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

**(7) Claims Appendix**

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

**(8) Evidence Relied Upon**

Marten et al. (Gastroenterol, 2002, 122, 406-414)

Weissleder et al. (Nature Biotech, 1999, 17, 375-378)

| | | |
|---|---|---|
| 6,610,269 | Klaveness et al. | 8-2003 |
| 6,008,373 | Waggoner et al. | 12-1999 |

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

Claims 15-18,20,21 and 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marten et al. (Gastroenterol, 2002, 122, 406-414) in view of Klaveness et al. (US 6,610,269B1 ) and further in view of Waggoner et al. (US 6,008,373).

Marten et al. (*Gastroenterol.* **2002**, *122*, 406-414) discloses cathepsin B sensing NIR fluorochrome probes comprising Cy5.5 (cyanine dye) containing cleavage sites, and a partially pegylated poly-L-lysine for imaging of the colon (p408, NIR fluorochrome probes; figure 2). The NIR fluorochrome probes are formulated for administration into mice (p408, NIR fluorochrome probes). Colonic adenomas can be visualized after injection of the NIRF probe into a mouse (figure 5) and colonic adenomatous polyps

ultimately lead to carcinoma formation and their detection has been shown to reduce the incidence of colorectal cancer. The probes are nonfluorescent in their native state but upon enzymatic cleavage the agent becomes fluorescent in the near-IR (figure 1; p412, paragraph 2). Marten et al. does not explicitly disclose that the NIR fluorochrome probes are pharmaceutical compositions comprising a pharmaceutically acceptable carrier which has a water solubility of at least 1mg/ml at pH 7.4 or that the contrast agents of the disclosure have a molecular weight of below 7,000 Daltons.

Klaveness et al. (US 6,610,269B1) discloses contrast agents of formula V-L-R where V is a vector moiety (i.e. peptide or non-peptide), L is a linker moiety (i.e. PEG) and R is a detectable reporter moiety/moieties (i.e. cyanine dye) for in vivo imaging (abstract; column 4, lines 10-20; column 5, lines 23-25; column 24, lines 56-58; column 28, lines 65+; column 42, line 40). The contrast agents of the disclosure are used for in vivo imaging of diseases associated with angiogenesis, such as colorectal cancer via administration with a physiologically acceptable carrier (column 3, line 27; column 4, line 53; column 56, lines 18-20). The linker moiety may contain 2-100 recurring units of ethylene oxide, have a molecular weight between 120 D to 20 kDa (column 33, line 1; column 36, lines 62-64) and also contain a biodegradable function which on breakdown can release the reporter from the vector (column 36, lines 14-18). Klaveness et al. teaches that the contrast agents have a targeting vector moiety which binds to receptors associated with angiogenesis (colorectal cancer), such as c-Met/hepatocyte growth factor receptor (Klaveness et al. column 1, lines 9-19; table 1).

Waggoner et al. (US 6,008,373) discloses that low molecular weight fluorescent labeling complexes/probes containing cyanine dyes, linkers and proteins have enhanced cell penetrating capabilities (abstract; column 2, lines 38-43). The fluorescent labeling complexes/probes having greater penetration into cellular environments have molecular weights of 500 to 10000 Daltons, and for a two fluorochrome complex, preferably in the range of 1000 to 2500 Daltons (column 3, lines 1-5; column 6, lines 15-22).

At the time of the invention it would have been obvious to one ordinarily skilled in the art to minimize the molecular weight of the fluorochrome probes of Marten et al. to 500 to 10000 Daltons (which includes below 7,000) or 1000 to 2500 Daltons (below 7,000) for a two fluorochrome complex by minimizing the linker molecular weight or the number of detectable reporter moieties to provide for probes having greater penetration into cellular environments. Also, the principles of cell penetration that apply in the imaging of isolated cells, such as that of Waggoner et al. would apply to imaging of cathepsin B or c-Met done either *in vitro* or *in vivo.*

Klaveness et al. teaches that cyanine contrast agents, peptide-PEG-cyanine dye, may be formulated in a physiologically acceptable carrier to generate pharmaceutical agents for vivo imaging and therefore it would have been obvious to one skilled in the art to formulate the cyanine contrast agents of Marten et al. in a pharmaceutically acceptable carrier as both disclosures are drawn to in vivo imaging of the colon with cyanine contrast agents. Thus, the contrast agents/probes of the combined disclosures are useful for imaging the colon as they can provide for real time imaging that may have

a significant impact on diagnosis of a very early stage of intestinal disease (Marten et al. p414, paragraph 4).

The contrast agents/probes of the instant claims do not provide any structural limitations over the prior art. Therefore, the contrast agents/probes of the combined disclosures encompass those of the instant claims and are capable of the same functions and have the same properties, such as a water solubility of at least 1 mg/ml at pH 7.4. Therefore, if the prior art teaches the composition or renders the composition obvious, then the properties are also taught or rendered obvious by the prior art. In re Spada, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990.) See MPEP 2112.01. The burden is shifted to Applicant to show that the prior art product does not possess or render obvious the same properties as the instantly claimed product.

Claims 15-18,20,21 and 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weissleder et al. (Nature Biotech, 1999, 17, 375-378) in view of Klaveness et al. (US 6,610,269B1 ) and further in view of Waggoner et al. (US 6,008,373).

Weissleder et al. (*Nature Biotech.* **1999**, *17*, 375-378) discloses NIRF probes for in vivo imaging comprising poly-L-lysine, MPEG and Cy5.5 (cyanine dye) (abstract; p375, paragraph 4). The NIRF probes of the disclosure are enzymatically activatable, thus producing fluorescence upon enzymatic cleavage (p375, paragraphs 2, 4 and 5). The NIRF probes were internalized into colon adenocarcinoma via uptake through fluid phase endocytosis thus indicating the feasibility of using these for the detection of

primary tumors in the colon, such as colon cancer (p376, paragraph 1; p377, paragraph 1). Weissleder et al. does not explicitly disclose that the NIR fluorochrome probes are pharmaceutical compositions comprising a pharmaceutically acceptable carrier or that the contrast agents of the disclosure have a molecular weight of below 7,000 Daltons.

Klaveness et al. (US 6,610,269B1) discloses contrast agents of formula V-L-R where V is a vector moiety (i.e. peptide or non-peptide), L is a linker moiety (i.e. PEG) and R is a detectable reporter moiety/moieties (i.e. cyanine dye) for in vivo imaging as well as that stated above.

Waggoner et al. (US 6,008,373) discloses that low molecular weight fluorescent labeling complexes/probes containing cyanine dyes, linkers and proteins have enhanced cell penetrating capabilities (abstract; column 2, lines 38-43). The fluorescent labeling complexes/probes having greater penetration into cellular environments have molecular weights of 500 to 10000 Daltons, and for a two fluorochrome complex, preferably in the range of 1000 to 2500 Daltons (column 3, lines 1-5; column 6, lines 15-22).

At the time of the invention it would have been obvious to one ordinarily skilled in the art to minimize the molecular weight of the fluorochrome probes of Weissleder et al. to 500 to 10000 Daltons (which includes below 7,000) or 1000 to 2500 Daltons (below 7,000) for a two fluorochrome complex by minimizing the linker molecular weight or the number of detectable reporter moieties to provide for probes having greater penetration into cellular environments. Also, the principles of cell penetration that apply in the

imaging of isolated cells, such as that of Waggoner et al. would apply to imaging of cathepsin B or c-Met done either *in vitro* or *in vivo*.

Klaveness et al. teaches that cyanine contrast agents, peptide-PEG-cyanine dye, may be formulated in a physiologically acceptable carrier to generate pharmaceutical agents for vivo imaging and therefore it would have been obvious to one skilled in the art to formulate the cyanine contrast agents of Weissleder et al. in a pharmaceutically acceptable carrier as both disclosures are drawn to in vivo imaging of the colon with cyanine contrast agents. Thus, the contrast agents/probes of the combined disclosures are advantageous for imaging the colon for the detection of the early stage tumors *in vivo* (Weissleder et al., abstract).

The contrast agents/probes of the instant claims do not provide any structural limitations over the prior art. Therefore, the contrast agents/probes of the combined disclosures encompass those of the instant claims and are capable of the same functions and have the same properties, such as a water solubility of at least 1 mg/ml at pH 7.4. Therefore, if the prior art teaches the composition or renders the composition obvious, then the properties are also taught or rendered obvious by the prior art. In re Spada, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990.) See MPEP 2112.01. The burden is shifted to Applicant to show that the prior art product does not possess or render obvious the same properties as the instantly claimed product.

**(10) Response to Argument**

Appellant asserts that Marten et al., Klaveness et al., and Waggoner et al. do not disclose, teach or suggest using c-Met. Hence, Appellants contend that no combination

of those references could provide the subject matter of the present claims. In addition, as already acknowledged by the Examiner in an Office action September 24, 2007, the logical combination of those references teaches towards probes which target a different biological target, i.e. cathepsin B.

Klaveness et al. was used to teach of contrast agents of formula V-L-R where V is a targeting vector moiety (i.e. peptide or non-peptide), L is a linker moiety (i.e. PEG) and R is a detectable reporter moiety/moieties (i.e. cyanine dye) for in vivo imaging of diseases associated with angiogenesis, such as colorectal cancer. Klaveness et al. further teaches that the contrast agents have a targeting vector moiety which binds to receptors associated with angiogenesis (colorectal cancer), such as c-Met/hepatocyte growth factor receptor (Klaveness et al. column 1, lines 9-19; table 1).

Marten et al. was used to teach that the NIR fluorochrome probes comprising Cy5.5 and a partially pegylated poly-L-lysine are used to image colonic adenomatous polyps via binding to cathepsin B.

Therefore, at the time of the invention it would have been obvious to one ordinarily skilled in the art to utilize the contrast agents/probes of the combined disclosures to target c-Met/hepatocyte growth factor receptor or cathepsin B for the in vivo imaging of diseases associated with angiogenesis, such as colorectal caner as both c-Met an cathepsin B are implicated in the progression of colorectal tumors.

Appellant asserts that they refer to Marten et al., cited above where the same cathepsin B probe of Weissleder et al. is described. Figure 1 (page 408), and the

associated text makes it clear that the probe is activated by the enzyme action of cathepsin B.

Klaveness et al. was used to teach of contrast agents of formula V-L-R where V is a targeting vector moiety (i.e. peptide or non-peptide), L is a linker moiety (i.e. PEG) and R is a detectable reporter moiety/moieties (i.e. cyanine dye) for in vivo imaging of diseases associated with angiogenesis, such as colorectal cancer. Klaveness et al. further teaches that the contrast agents have a targeting vector moiety which binds to receptors associated with angiogenesis (colorectal cancer), such as **c-Met** hepatocyte growth factor receptor (Klaveness et al. column 1, lines 9-19; table 1).

Weissleder et al. was used to teach that the NIR fluorochrome probes comprising Cy5.5 and a partially pegylated poly-L-lysine are used to image colonic adenomatous polyps via binding to cathepsin B.

Therefore, at the time of the invention it would have been obvious to one ordinarily skilled in the art to utilize the contrast agents/probes of the combined disclosures to target c-Met/hepatocyte growth factor receptor or cathepsin B for the in vivo imaging of diseases associated with angiogenesis, such as colorectal caner as both c-Met and cathepsin B are implicated in the progression of colorectal tumors and are taught by Klaveness as art recognized equivalents in colorectal tumors.

**(11) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Michael G. Hartley/

Supervisory Patent Examiner, Art Unit 1618

Conferees:

/Melissa Perreira/

Examiner, Art Unit 1618

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627